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CHEMICAL DEFENCE EXPERIMENTAL ESTABLISHMENT

CHANGES IN CARDIAC OUTPUT FOLLOWING THE ADMINISTRATION OF SARIN AND OTHER PHARMACOLOGICAL AGENTS.

PART I.

THE DETERMINATION OF CARDIAC OUTUT BY MEANS OF THE LOW-FREQUENCY BALLISTOCADIOGRAPH

BY

R.J. SHEPHARD

PORTON TECHNICAL PAPER No. 734

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Porton
Wilts.

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SUMMARY

1. Methods of measuring human cardiac output involving minimal discomfort to the subject are reviewed, and it is concluded that the ballistocardiograph (B.C.G.) is the best available method of studying cardiac output over long periods.

2. The physical theory of four B.C.G. Systems is discussed in terms of Newton's laws of motion. Analysis is complicated by three-dimensional movement of blood, extraneous body movements, variations in body/table coupling, in-phase movements of chest and viscera, and superimposition of successive waves.

3. Reasons are given for selecting the Nickerson low-frequency critically damped B.C.G. to measure cardiac output, and a formula for calculating relative stroke volume is presented.

4. Modifications of the Nickerson B.C.G. are described for the recording of cardiac output in man and the dog, and the correlation between B.C.G. and other methods of measuring cardiac output is discussed.

5. It is concluded that the B.C.G. requires independent verification, particularly where large changes of blood pressure occur. Since this cannot conveniently be done in man, it is suggested that the B.C.G. should be calibrated against direct flow measurements in the dog, and if the two methods agree in the test situation, then the human B.C.G. data may be accepted with fair confidence.

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I. INTRODUCTION

In studying the cardiovascular effects of anticholinesterase agents, as in many problems of applied physiology, there is a need for a simple yet reliable method of assessing continuously any changes in the cardiac output of the conscious human. The subjects available are typically untrained in physiological procedures, and are only available for a few days. Further, as volunteers with a non-medical background, they cannot be subjected to manoeuvres involving more than a minimum of discomfort. Many methods of measuring cardiac output have been suggested in the past few years, but most fail to meet the requirements of this situation:

1. Pulse-pressure method.

This was introduced in Germany (1) and has recently been rehabilitated and simplified by application of analogue computing techniques (2). A continuous indication of cardiac output is obtained, but puncture of a major artery by a wide-bore needle is required to give valid results.

2. Impedance cardiography

Changes in the electrical impedance of the trunk were at first thought to yield a useful continuous record of cardiac output (3), but more recent work has shown that changes of impedance are marginal, being largely counteracted by an increased impedance in the peripheral part of the trunk and limbs (4).

3. Dye dilution

Although this method checks well against direct measurements of cardiac output (5), in most applications of the method very few

determinations can be made because of a progressive pigmentation of the subject. Further, despite advances in oximetry (6), it is generally admitted that arterial puncture is needed for reliable mixing curves.

A modification of the dye method using an external scintillation counter mounted over the great vessels of the chest was introduced by Veall (7). An accuracy similar to that of the direct Fick method has been claimed, but the radiation dosage (0.07 - 0.28r for one determination of cardiac output) is such as to prohibit repetitive studies.

4. Foreign gas methods

The acetylene method has become simpler and subjectively more pleasant with the introduction of infra-red gas analysis (8, 9), but the time required for elimination of acetylene is such that observations cannot be made more frequently than once in every half an hour. Other gasometric methods involving the rebreathing of nitrous oxide (10) or various carbon dioxide mixtures (11) require considerable co-operation from the subject, and again give no more than a single isolated value for cardiac output.

5. Electrokymography

Although it has been suggested that a continuous record of cardiac output can be obtained by positioning photo-multiplier tubes over the left border of the cardiac shadow on an X-Ray screen, displacement, torsion, and change in contour of the heart combine to make this an unsatisfactory method (12). With repeated measurements, the subject is also exposed to an undesirable radiation load.

6. Ballistocardiography

The fact that the forces developed by the heart can be recorded by a suitably mounted table has been known for many years (13, 14), but application of this principle to cardiac output determinations is due largely to Nickerson (15) and Starr (16). The ballistocardiograph (B.C.G.) gives a continuous record, and requires no more of the subject than to lie reasonably still on a hard table. Although the measurement of cardiac output by this technique is still controversial, it is probably the best method at present available to the applied physiologist who wishes to study cardiac output continuously for an hour or more.

The purpose of this first paper is to review the technique of ballistocardiography, indicating specific criticisms of the method, and in the light of this criticism to suggest a procedure whereby results from the B.C.G. may be verified.

II. PHYSICAL THEORY

Four main types of B.C.G. may be distinguished:

(a) High frequency: developed by Starr and his associates, (16), with a natural frequency of 15 c.p.s.

(b) Low frequency: critically damped, as developed by Nickerson (15) the natural frequency being 1-1½ c.p.s.

(c) Ultra low frequency and "aperiodic" systems, as developed by Scarborough and associates (17) and Burger and associates (18).

(d) Direct body pick-up as developed by Dock (19)

The relationships between the several types of B.C.G. can best be explained in terms of the fundamental Newtonian equation for forces in the longitudinal direction at the instant of cardiac ejection:

$$m\frac{d^2y}{dt^2} = M\frac{d^2x}{dt^2} + C\frac{dx}{dt} + Dx \qquad \ldots\ldots (1)$$

where m is the mass of blood ejected, y the longitudinal displacement in time t, M the mass of subject and table, x the displacement of the table, C is a damping constant assumed proportional to velocity, and D is an elastic restoring constant proportional to displacement. In the Starr bed, the restraining force D is large, and damping C and acceleration small, so that the equation reduces to

$$m\frac{d^2y}{dt^2} = Dx$$

or

$$x = \frac{m}{D}\frac{d^2y}{dt^2} \qquad \ldots\ldots (2)$$

The Nickerson bed has a restraining force D, but the most important factor in the system is the damping C introduced by an oil bath*. To a first approximation, the equation reduces to

$$m\frac{d^2y}{dt^2} = C\frac{dx}{dt}$$

or

$$x = \frac{m}{C}\frac{dy}{dt} \qquad \ldots\ldots (3)$$

*At frequencies in excess of 6 c.p.s., D becomes progressively more important, and the pattern of the record changes to a second order integration. However, the amplitude at this end of the frequency spectrum is negligible (20).

The ultra-low frequency beds (19) have very weak constraints, and only the first term in the equation is of importance. Thus

$$m\frac{d^2y}{dt^2} = M\frac{d^2x}{dt^2}$$

or $$x = \frac{my}{M} \qquad \ldots\ldots (4)$$

Direct body systems have a less certain mechanical basis, simply recording movements of the shins with respect to the dorsal fat pad. The recording system normally used (19) is further complicated by a small "integrating" condensor and while the tracings are useful for diagnostic work precise physical analysis is not possible. Typical records appear to be intermediate in form between velocity and displacement tracings.

III. COMPLICATING FACTORS

In practice, several factors complicate the above physical analysis of table movement:

(a) Plane of recording

Consideration of the forces developed by the heart has so far been restricted to the longitudinal plane. In fact, the path of blood ejected from the ventricles is directed somewhat laterally and posteriorly, and vector ballistocardiograms (21-23) have shown that appreciable forces are developed in the lateral plane. The relative magnitude of the lateral component must vary with cardiac axis, and although the problem may be minimised by averaging the longitudinal force over several respiratory cycles, a shift of mean cardiac axis could still produce an apparent change of cardiac output in uniplanar B.C.Gs.

(b) Extraneous movements

Any type of table will respond to extra cardiac movements of the body or viscera. The average adult subject can be persuaded to restrain voluntary movements during the recording period, but involuntary tremor (due to cold or pharmacological agents) and coughing (common with some CW agents) can distort sections of record. Respiratory movements also affect the amplitude of deflections, for although the normal frequency of respiration is considerably less than that of the events under investigation, the mass of the displaced viscera is large relative to the mass of ejected blood; when this is in phase with visceral movement, deflections become larger. This problem can be overcome by averaging over the respiratory cycle.

(c) Body coupling

The simple Newtonian equation assumes that the body and table have homogenous properties, and that they are rigidly

coupled together. In fact, the body is coupled rather loosely to the table by a dorsal fat pad that varies in mechanical properties from subject to subject, and the heart is also loosely coupled to the remainder of the body. Thus the ratio of body/table movement is rather large with all B.C.G. systems, although it may be improved by damping and by head or foot rests exerting a force of up to 25 kg (26). Furthermore, the system is not mechanically homogenous. Body damping (50% critical) and frequency (5-9 c.p.s.) do not conform with any of the commonly used B.C.G. systems (24). The theoretical aspects of body coupling have been explored in detail (25-27); errors may arise from resonance peaks and phase shifts. Over the vital range of 1-5 c.p.s., the Starr B.C.G. gives negligible phase shift, but table, table/body, and body/heart movement all show large resonance peaks. The Nickerson B.C.G. gives a large phase shift (almost 180°), but this is relatively constant over a wide frequency range; amplitude of table and table/body movement is also recorded with only slight distortion to 5 c.p.s., although higher frequencies are progressively attenuated. The Burger B.C.G. (ultra-low frequency) introduces some distortion of amplitude and phase at 1-2 cps, although with the addition of careful damping (40% critical) such effects can be minimised. The practical consequence of these findings is that the main waves of the B.C.G. (fundamental frequency 2 c.p.s.) are recorded most faithfully by the Nickerson bed. The amplitude of one or more of these primary waves is normally used in the determination of cardiac output, and the Nickerson bed is therefore to be preferred for this purpose. With other B.C.G. systems, a change in the rate of cardiac ejection, by altering the fundamental frequency of oscillation, can of itself change the amplitude and simulate an alteration of cardiac output.

(d) Superimposition of waves

While the Newtonian equation describes events at the instant of cardiac ejection, the resultant longitudinal force is soon modified by reversal of flow in the arch of the aorta and at the bifurcation of the pulmonary artery, and by an increase in the dimensions of the arterial tree with the pulse wave. The rate at which these secondary factors appear can obviously vary with physiological state, and while a correction term has been evolved for flow reversal (28), calculation is tedious.

With normal pulse rates, there is a brief interval in each cardiac cycle that is free of oscillations, but when the heart rate increases, the later waves from one cycle may become superimposed on the early part of the next cycle. Interference between successive cardiac cycles is less in a critically damped system, but even with the Nickerson B.C.G. it is difficult to obtain meaningful records at pulse rates in excess of 120-130/min.

IV. CHOICE OF B.C.G. AND FORMULA FOR CARDIAC OUTPUT MEASUREMENTS

While it is apparent from the foregoing that no B.C.G. technique for the estimation of cardiac output is free of difficulties, a number of facts such as the spectrum of frequency response and reduced interference between successive cardiac cycles suggest that the Nickerson bed is to be preferred if the B.C.G. is used for this purpose.

It has been shown theoretically that the Nickerson B.C.G. gives predominantly a velocity record (equation 3), and the tracings obtained in this laboratory agree well with velocity curves predicted from the physical properties of the arterial tree (Fig.1, ref. 29). Tracing A is the predicted curve, tracing B the observed curve with a simultaneous praecordial phonocardiogram. Tracings C and D were obtained in the dog, and will be discussed later (page 9). Immediately following the first heart sound, both tracings show a sharp footward movement of the table (the I wave) corresponding with ejection of blood into the ascending aorta. This is followed by a larger headward movement of the table (J wave), coinciding with flow reversal in the arch of the aorta, slowing of ejection, and enlargement of the aorta. A third prominent (M) wave follows the second heart sound; this is generally considered due to reflection of the pulse wave in the periphery of the arterial tree.

Cardiac output determinations are usually based on the IJ amplitude, mainly because the I and J waves are large and sharply defined. Attempts have been made to translate IJ amplitude into absolute cardiac output, but even if possible this does not seem either necessary or desirable, since the apparatus is best restricted to comparative work. Further, the standard calibrating system (pulley and weights) is essentially a static force, corresponding with the term Dx of the fundamental equation 1. Calibration carried out in this way serves as a useful check on the stability of amplifiers and recording system, but does not provide any measure of momentum that can be used for the calculation of blood flow in absolute terms[*]. In the present work, use has been made of a simple empirical formula:

$$\text{Relative stroke volume} = \frac{\text{IJ amplitude} \times \text{Blood Pressure factor}}{\text{IJ time}} \quad \ldots (5)$$

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[*]C is deliberately varied by the operator in inverse proportion to the body mass of the subject. D tends to vary in direct proportion to body mass, and is also affected by the elasticity of the dorsal body fat. There is thus no constant relationship between the values for C and D in different subject.

This bears some similarity to Nickerson's empirical formula (30). The IJ amplitude has already been defined, and the IJ time is the corresponding interval between the trough of the I and the crest of the J waves. The blood pressure factor is introduced to allow for changes in the dimensions of the arterial tree. Nickerson has suggested the use of the square root of the mean systemic pressure, with certain empirical modifications where this mean pressure is less than 80 mm Hg. (Fig.2), but theoretical analysis indicates that a more appropriate factor is based on the square root of aortic volume at a given pressure:

Let the mass of the laden table be M

The mass of blood ejected in one cardiac cycle m

The average velocity of the blood during ejection $\dot{V}$

and the average velocity of the table (as indicated by IJ amplitude) x

Then from the conservation of momentum

$$(m + M)x = m\dot{V}$$

and

$$x = \left(\frac{m}{m+M}\right)\dot{V}$$

or since M is large with respect to m

$$x = \frac{1}{K}\, m\dot{V}$$

where K is a constant

Now if the aortic cross sectional area is A,

$$m = \dot{V}A$$

and

$$\dot{V}^2 = \frac{Kx}{A}$$

But stroke volume $V = \dot{V}A$

Thus $V^2 = KAx$ ..... (6)

and stroke volume is proportional to the square root of the aortic cross-sectional area. The relative cross-sectional area for a given mean aortic pressure can be obtained from Roy's pressure/volume curves (31). Over the normal working range of blood pressures, the factors obtained empirically by Nickerson correspond closely with factors derived from the square root of aortic cross-section, but at the extremes of pressure (where the B.C.G. is often said to be less accurate) considerable differences are observed (Fig.2). The use of factors derived from

Roy's P/V curve results in a better correlation of the B.C.G. with direct flow measurements than the use of Nickerson's empirical factor, and the P/V factor has therefore been used throughout the present study.

In equation (6), stroke volume is theoretically proportional to the square root of table displacement x, but in practice displacement x is used without transformation. This is partly because equation (6) is based on average impact velocity V, while the IJ waveform is derived from a continuously changing table velocity. The IJ amplitude is also much curtailed by superimposition of preceding and succeeding waves of opposite sign. However, the main justification for this step is empirical. Extensive trial of x and $\sqrt{x}$ by Nickerson and others has shown that x bears the closest correlation to directly determined cardiac output.

The IJ time is not introduced into the equation to convert displacement to velocity (as is apparently Nickerson's intention) for this differentiation is carried out by the mechanical system of the table. It is intended rather as a simple empirical correction for the increasing superimposition of successive ballistic waves with more rapid cardiac ejection.

Values for relative stroke volume obtained from equation (5) were averaged over two respiratory cycles to allow for undesirable respiratory variations due to changes in cardiac axis, body/heart coupling, and in-phase visceral movements. This was found preferable to the unphysiological procedure of breath-holding.

V. MODIFICATIONS OF NICKERSON LOW-FREQUENCY B.C.G.

The B.C.G. used in this laboratory (Fig.3) was built to the basic design of Nickerson and Curtis (15). An improved damping system permitted a light oil with low temperature coefficient (viscostatic Aeroshell Fluid 4) to circulate between two brass bellows via a micrometer operated conical valve. In any one subject the micrometer reading for critical damping was remarkably constant even when room temperature was deliberately varied by 8-10°C; in different subjects, the readings varied inversely with body weight (Fig.4). This may imply that the body tissues of a heavier individual are more nearly critically damped, but could also be a consequence of more effective body/table coupling with increase of body mass.

Movement of the table was sensed by an electronic valve transducer (R.C.A.5734), giving an essentially linear response over the permitted angular displacement of the anode. Static (recorder) calibration was by pulley and 200 g. weight. Provision was also made for dynamic calibration, using a solenoid operated time switch fitted with a tray carrying suitable weights. Both types of calibration gave very consistent deflections in a given subject, and it was therefore possible to use IJ amplitude, rather than a scaled derivative in the calculation of relative stroke volume (equation 5).

A scaled-down version of the human B.C.G. was developed to permit recording of the B.C.G. in the dog. Some account was taken of the differing physical properties of the two systems, (Table 1), but uncertainties

regarding differences of body damping and body/table coupling made the scaling largely expirical. The overall objective was to produce a table with a flat frequency/amplitude curve for the range 2-10 cps, to correspond with the higher fundamental frequency of the IJ wave. The stroke momentum is much smaller in the dog, and a corresponding reduction of bellows resistance in the damping system was thus introduced to permit adequate table movement. The stroke/table mass ratio is also usually less favourable, and it was therefore decided to make the table top of very light construction. Adequate friction to prevent excessive body/table movement was provided by a washable rough-surfaced acetate fibre board, and this was supported on an aluminium frame. The restoring force is relatively greater in the dog B.C.G., since this is proportional to the square of table frequency. Theoretically, this should cause the tracing to change from a first differential (velocity) pattern to a second differential (acceleration) pattern at a relatively lower frequency. In practice the B.C.G. tracings that have been obtained in the dog (Fig.1) are quite similar in form to the human B.C.G. Tracing C shows the B.C.G. and carotid pulse with a relatively low blood pressure, tracing D the B.C.G. and carotid pulse during systemic hypertension. Timing of individual waves is less easy with the more rapid pulse of the dog, but there is some suggestion that the main peaks occur earlier in the cardiac cycle, which is a characteristic of transition to an acceleration pattern.

VI. CORRELATION BETWEEN B.C.G. AND OTHER METHODS OF MEASURING CARDIAC OUTPUT

Many previous investigators have studied the degree of correlation between the cardiac output calculated from B.C.G. records and results obtained by the direct Fick or other non-controversial methods. Richards and his colleagues (32) found no significant correlation, but most other workers (30, 33, 34) have stated that in the normal healthy subject under resting conditions, the B.C.G. gives a reliable value for cardiac output. Agreement with the acetylene method has been observed over a wide range of blood pressures (35), although in severe "shock" (36) and aortic insufficiency (30) discrepancies were noted. With administration of norepinephrine (37) and nitroglycerine (38)., the B.C.G. gave an incorrect indication of the direction of change of cardiac output. It is evident that the B.C.G. amplitude is dependent not only on the mass of blood ejected, but also upon the tone and dimensions of the arterial tree into which ejection is occurring. Since the condition of the arterial tree is not measured*, during the investigation, absolute values for the cardiac output derived from the B.C.G. must always be of doubtful significance. Relative values for cardiac output may be more reliable, especially if there are no large changes of systemic blood pressure during the test; however, even relative changes require confirmation by some independent method, particularly in the study of a new pharmacological

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*The blood pressure factor (discussed on page 7) does make some allowance for variations in the physical properties of the arterial tree when systemic blood pressure is reduced.

agent with unknown actions on other parts of the vascular system.

VII. METHOD OF VERIFYING B.C.G. CARDIAC OUTPUT DATA

As indicated in the introduction, direct calibration of the B.C.G., for example by carrying out simultaneous direct Fick determinations of cardiac output, was not thought justified in service volunteers. A more indirect calibration procedure was therefore adopted. Unequivocal measurements of blood flow were obtained in the dog by inserting a venturi tube in the aorta, and the results were compared with simultaneous records from the critically damped low-frequency B.C.G. designed for the dog. The dog could be exposed to much larger doses of Sarin and other pharmacological agents than the human subjects, and having shown that the B.C.G. gave reliable qualitiative information during exposure to large doses, it was thought reasonable to accept smaller changes of cardiac output indicated by the B.C.G. in human experiments at low dosage levels.

A similar approach has been developed independently by Honig and Tenney (39) in Rochester, N.Y. They have built a lower frequency table (0.5 c.p.s.) with heavy damping, and have compared B.C.G. records with aortic flow measured by a hydrometric pendulum during controlled haemorrhage and administration of "neosynephrine".

The results of the present author's calibration trials in the dog are reported in P.T.P.735, Part 2 of this series of reports.

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Table 1

Comparison of Ballistocardiograph Mechanics in Dog and Man

	Dog	Man
Fundamental frequency (cps)		
Body tissues	3	5
Cardiac cycle	2.5	1.25
Respiratory cycle	0.5	0.25
IJ wave	5.0	2.5
Table	3	1.5
Mass (Kg)		
Body tissues	10-20	70
Table (unladen)	2	17
Table (laden)	12-22	87
Force		
Cardiac output (l/min)	1-2	7
Stroke volume (ml)	4-16	60-100
Stroke momentum (g.cm/sec)	80-600	2400-4000
Ratio Stroke/table mass (10^{-3})	0.2-1.3	0.9-1.3
Restoring force (lb/in.)	25	40
Damping bellows (lb/in.)	0.5-1	5

Fig.1: Comparison of theoretical and observed B.C.G. velocity records

(A). Theoretical form of B.C.G. wave predicted from properties of arterial tree, showing I, J, and M waves and timing in relation to heart sounds.

(B) Observed B.C.G. record in human subject, with simultaneous phonocardiogram.

(C). Observed B.C.G. and carotid blood pressure records from dog with low blood pressure.

(D) Observed B.C.G. and carotid blood pressure records from dog with high blood pressure following administration of pressor amines.

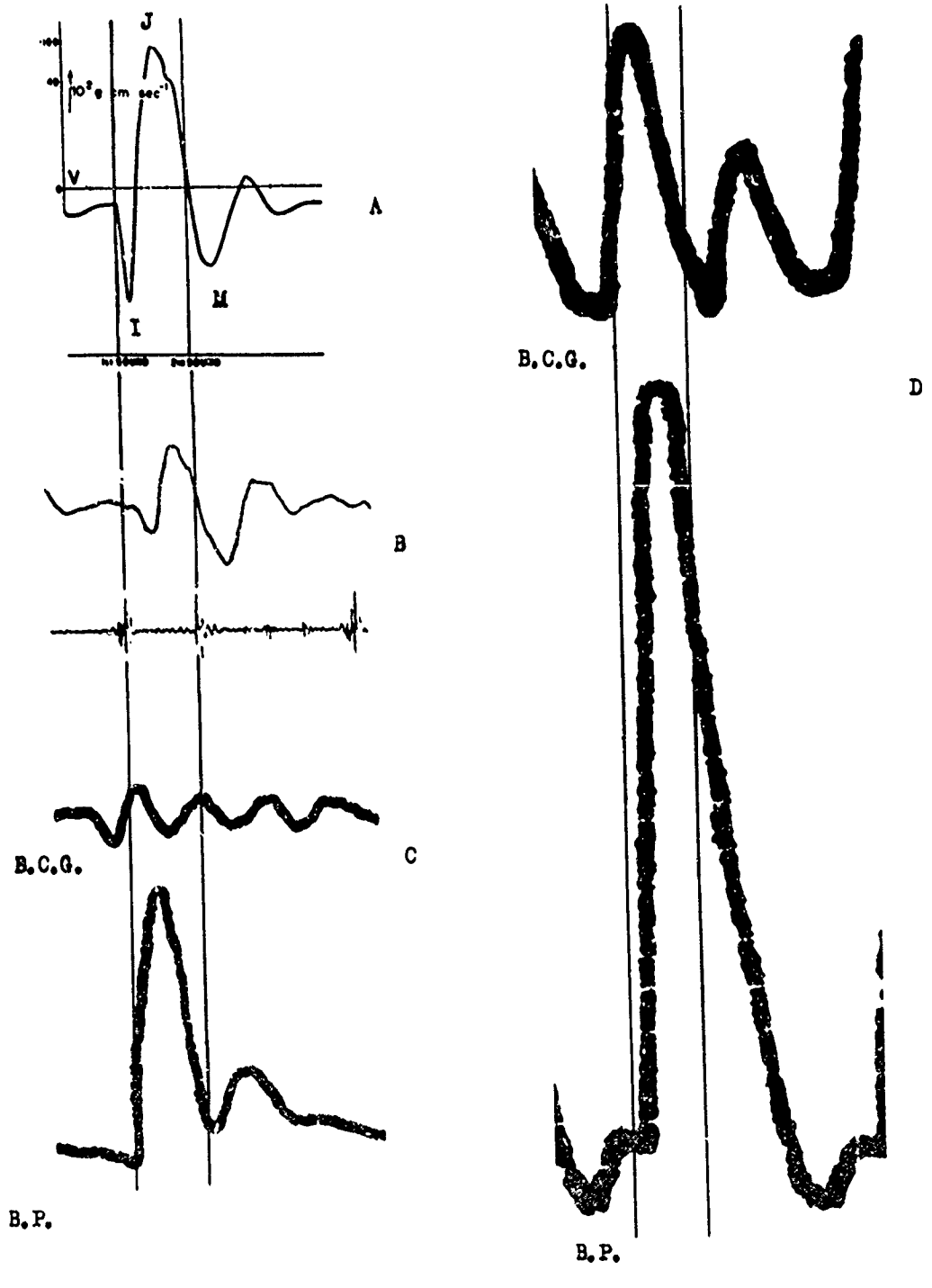

FIG. I.

P.T.P. 734.

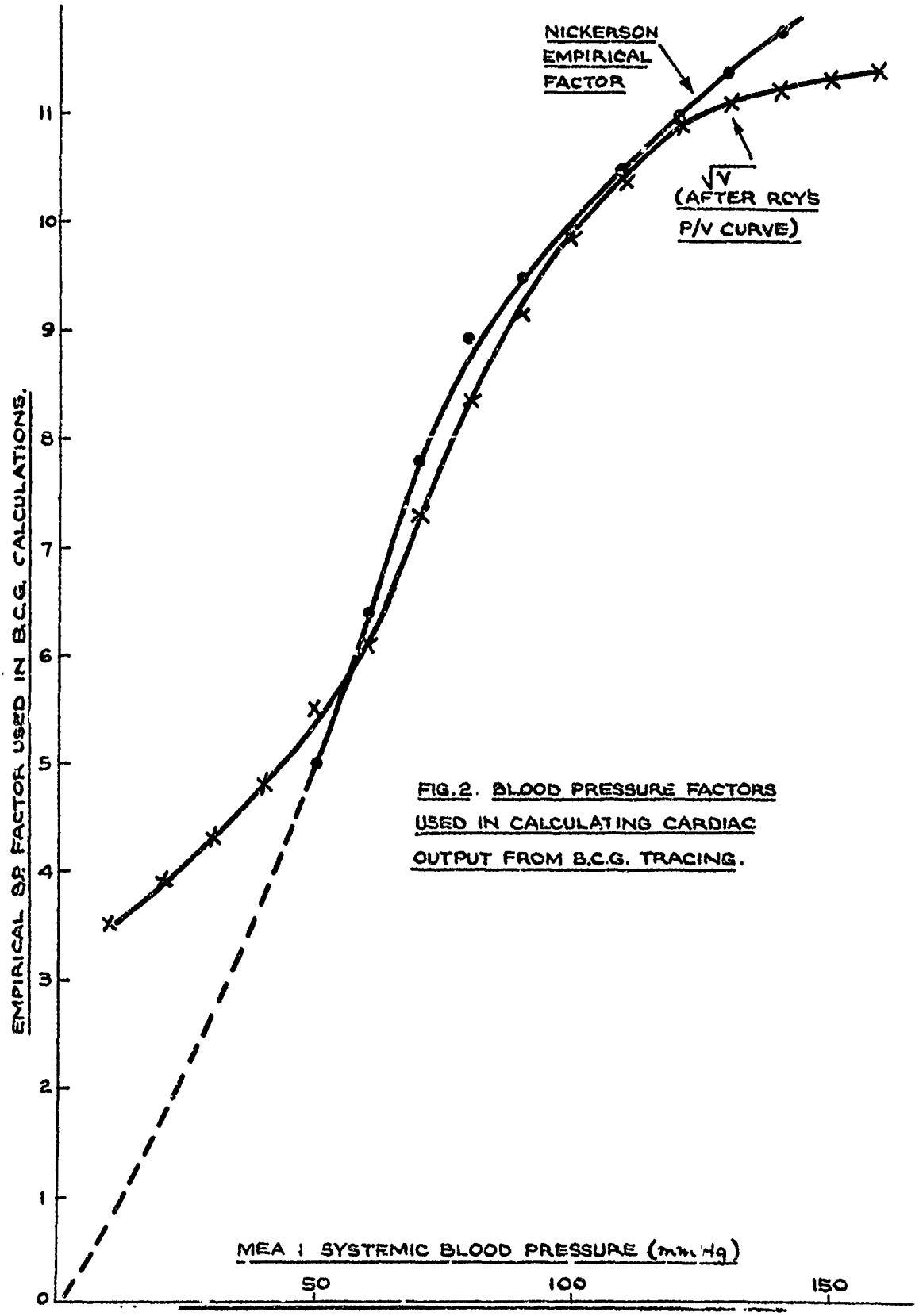

FIG. 2. BLOOD PRESSURE FACTORS USED IN CALCULATING CARDIAC OUTPUT FROM B.C.G. TRACING.

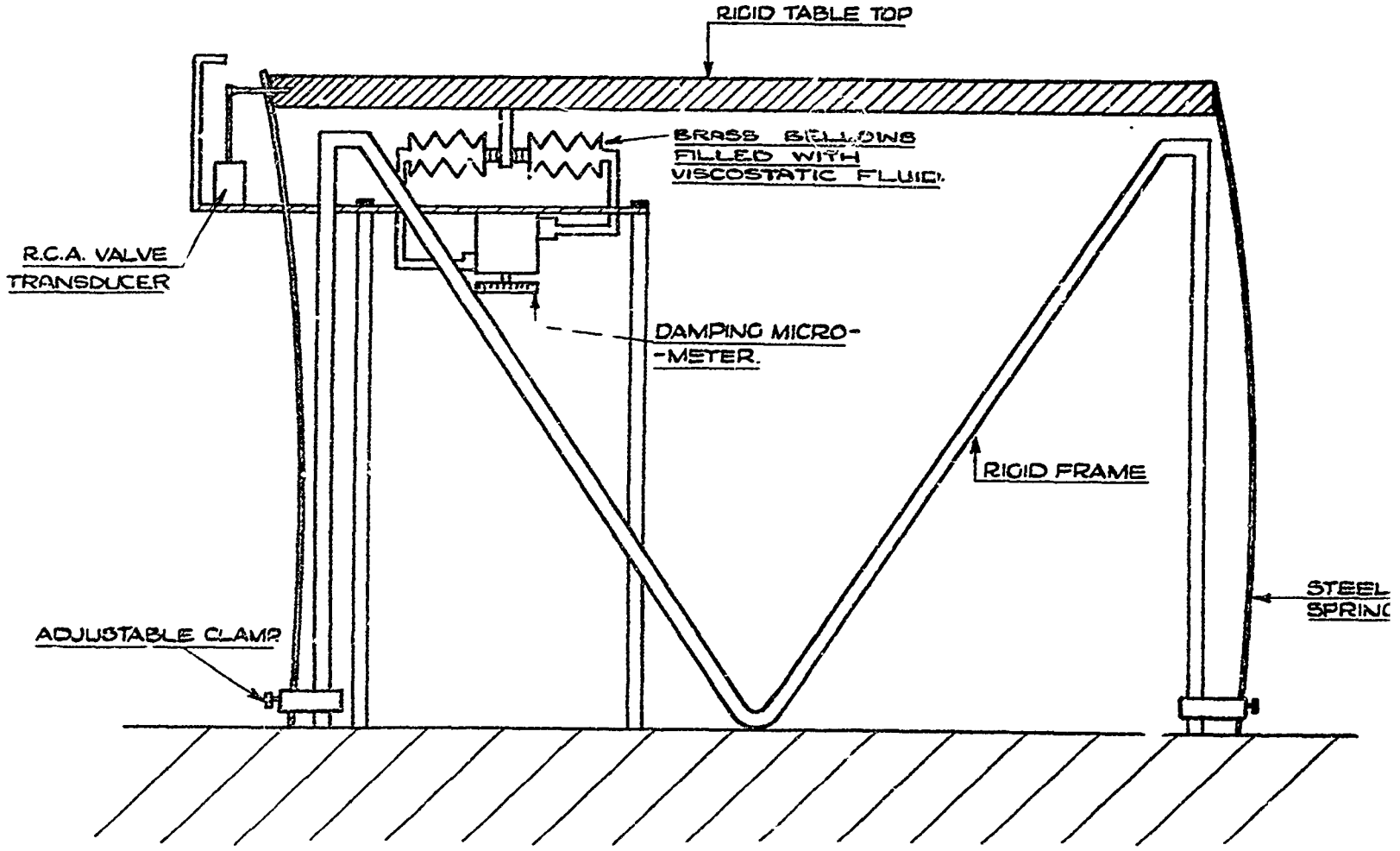

FIG. 3(c) DIAGRAM OF CRITICALLY-DAMPED LOW FREQUENCY B.C.G.

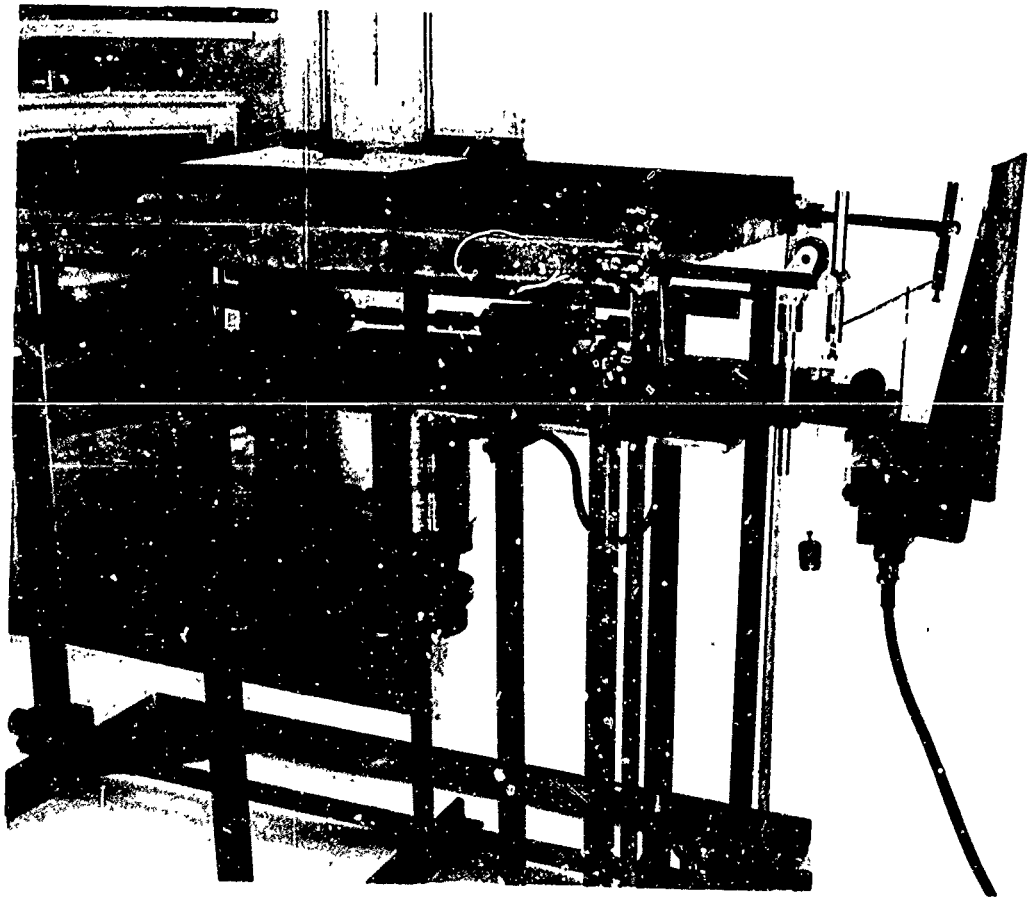

Fig. 3(b). Close-up view of dog S.C.C., giving details of damping system and R.C.A. valve mounting.

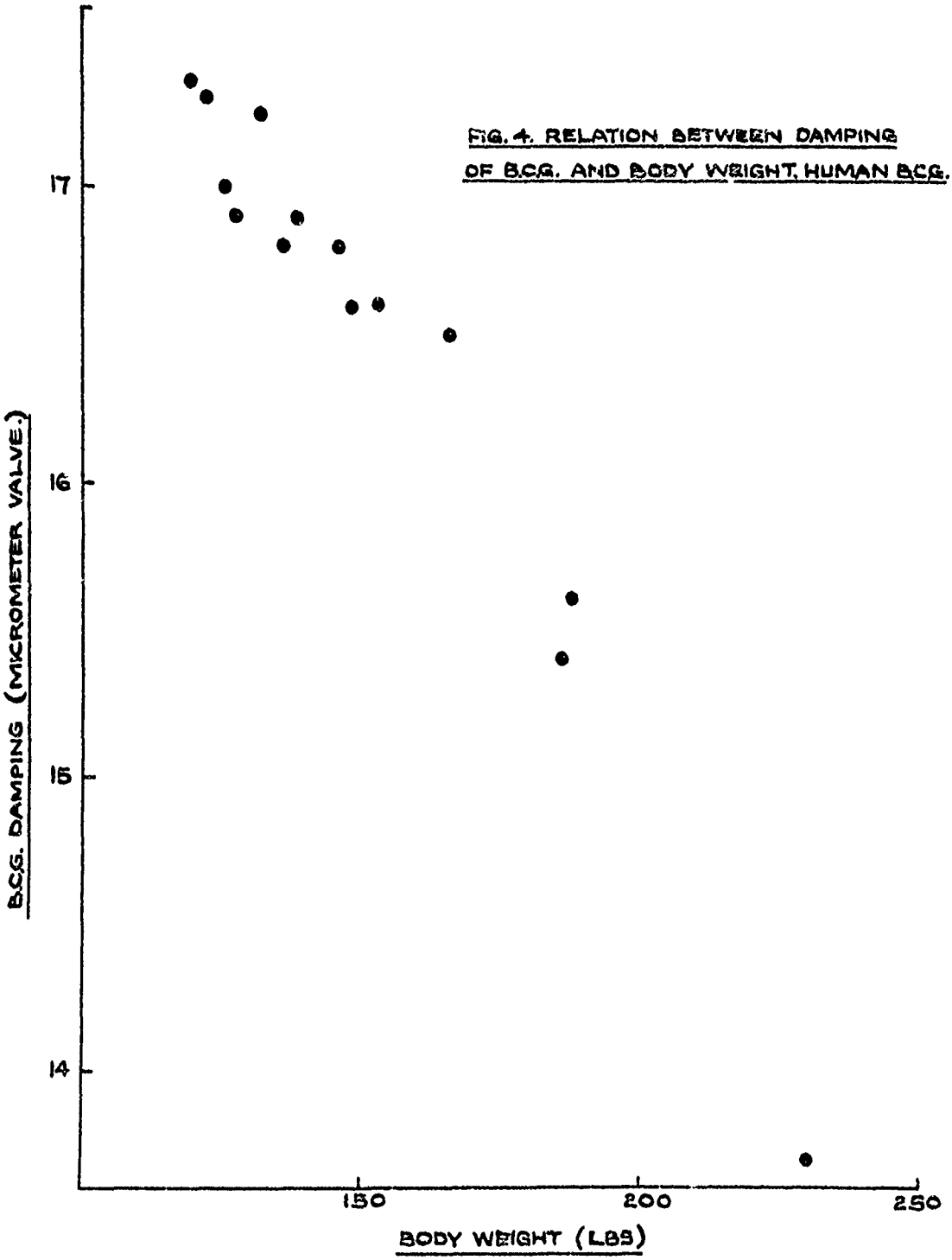

FIG. 4. RELATION BETWEEN DAMPING OF B.C.G. AND BODY WEIGHT, HUMAN B.C.G.

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